REFERENCES

1. DOLL, R. AND HILL, A. B.: *Brit. M. J.*, 2: 739, 1950.
2. WYNDER, E. L. AND GRAHAM, E. A.: *J. A. M. A.*, 143: 329, 1950.
3. DOLL, R.: *In*: Symposium on the Endemiology of Cancer of the Lung, Louvain, 1952, edited by J. Clemmesen, Council for International Organizations of Medical Sciences, Paris, 1953, p. 69.
4. KENNAWAY, E. L. AND WALLER, R. E.: *Ibid.*, p. 59.
5. WELLER, R. W.: *Am. J. Clin. Path.*, 23: 768, 1953.
6. NISKANEN, K. O.: *Acta path. et microbiol. scandinav., Suppl.*, 80: 1, 1949.
7. LINDBERG, K.: *Arb. a. path. Inst. d. univ. Helsingfors*, 9: 1, 1935.
8. LIEBOW, A. A.: *In*: Armed Forces Institute of Pathology, Atlas of tumor pathology—tumors of the lower respiratory tract, Washington, D.C., 1952, Fasc. 17, pp. 16 and 63.
9. AUERBACH, O. *et al.*: *Cancer*, 9: 76, 1956.
10. WITTEKIND, D. AND STRÜDER, R.: *Frankfurt. Ztschr. Path.*, 64: 294, 405, 1953.
11. WELLER, C. V.: Causal factors in cancer of the lung, Charles C Thomas, Springfield, Ill., 1956.
12. BLACK, H. AND ACKERMAN, L. V.: *Ann. Surg.*, 136: 44, 1952.
13. MCGRATH, E. J., GALL, E. A. AND KESSLER, D. P.: *J. Thoracic Surg.*, 24: 271, 1952.

RÉSUMÉ

L'arbre bronchique du poumon droit de 65 sujets fut soumis à l'examen histopathologique. Dans les cas où ce poumon était cancéreux, l'autre fut examiné. Les sujets divisés en trois catégories, comprenaient 30 cas de cancer du poumon, 15 fumeurs dont les poumons n'étaient pas cancéreux et 20 non-fumeurs. Cinq genres de modification de l'épithélium furent observés: une hyperplasie basocellulaire, de la stratification, de la métaplasie pavimenteuse, de la métaplasie de transition et des altérations intermédiaires. L'observation la plus fréquemment notée fut l'hyperplasie basocellulaire qui prit plus d'ampleur et fut retrouvée avec une fréquence distinctement plus marquée chez les fumeurs, y compris ceux qui avaient un cancer, que chez les non-fumeurs. Les autres altérations ne furent que légèrement plus fréquentes dans le premier groupe. A l'exception de l'hyperplasie basocellulaire les altérations décrites dans l'épithélium bronchique se retrouvent dans l'inflammation chronique des bronches. Cependent l'ampleur et la fréquence accrue de cette hyperplasie basocellulaire dans les poumons cancéreux et dans ceux des fumeurs ne peut s'expliquer par une cause inflammatoire. Ces résultats semblent confirmer des observations antérieures faites à ce sujet et justifier une étude plus approfondie.

THE VALUE OF CHLOROQUINE IN RHEUMATOID DISEASE
A FOUR-YEAR STUDY OF CONTINUOUS THERAPY

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THE TREATMENT of rheumatoid disease with adrenal glucocorticoids has made it very clear that what is still required for its successful management is a drug that will control the systemic disease itself, not merely the inflammation in the target-organs, i.e. the joints. The ideal for long-term control would be a drug of very low toxicity, to which tolerance does not develop—so that it may be given safely and effectively over the many years of ebbing-and-flowing inflammatory activity that characterize the natural history of the average case of rheumatoid arthritis.

Parenteral gold was the first agent that appeared to arrest the systemic disease itself—but the rather high incidence of toxicity made it of long-term value in only a small proportion of patients. The data to be presented herein suggest that chloroquine may be the best approach at present available towards the ideal drug for the long-term management of rheumatoid arthritis, including the prophylaxis of relapses.

MATERIAL

One hundred and twenty-five private patients with rheumatoid disease have been carefully followed up personally, some of them for over four years after chloroquine therapy was instituted.

The aim was to keep them on continuous therapy for at least a year longer than the disease had existed at the start of chloroquine therapy, in the same fashion as the author had previously employed parenteral gold.

Four patients had less than six months' treatment but are included because toxicity necessitated withdrawal. All the rest had eight months or more of continuous therapy, 75% for more than one year, 50% for more than two years and 20% for more than three years.

During the first two years of this trial, only serious "problem" cases were chosen but, since then, all patients seen in whom a firm diagnosis of rheumatoid disease could be made, were started at once on chloroquine. Thus 55 (45%) had been under other (intensive) treatment for more than four months and up to six years before chloroquine, while 55% had less than five months' prior treatment. Of the 125 patients, 94 (75%) are still under treatment at the time of analysis (and 90% of those still under treatment show Grade I or II improvement). None of these 125 patients has been lost, so that the study is complete.

Double-blindfold study: In November 1953, a "double-blindfold" study of chloroquine (Aralen*) was instituted. By that time, I had gained a very favourable impression of its value and did not feel that I could ethically substantiate administration of the placebo to seriously affected patients with rheumatoid arthritis for some months. As a result, this additional group of cases is limited to those with a relatively mild, but very persistent type of rheumatoid disease. A much larger study was instituted at the same time in the various Arthritis Clinics in Vancouver, but is not reported here because the cases were not followed up personally.

The plan of "double-blindfold" study was to place alternate patients on capsule A and capsule B. At the end of two months, the initial capsule was continued if there was improvement. If there was no improvement, a switch was made to the other capsule for two months, or more if improvement ensued. Eleven patients were started on capsule A and ten on capsule B. One patient in each group failed to return for review; the rest were adequately followed up.

METHOD OF TREATMENT

Drug: Bitter, white, scored tablet of 250 mg. of chloroquine diphosphate (Aralen)—60% chloroquine alkaloid, by weight.

Dosage: 250 mg. (0.25 gram) tablet once daily. This dose was empirically selected for long-term use because it was known that (a) 0.5 g. weekly is easily tolerated for malaria prophylaxis, and (b) 0.5 g. daily for 3-4 weeks is "usually well tolerated" in the treatment of amœbiasis.

Timing of dosage: Originally, the 0.25-g. tablet was given with breakfast so that it would be least likely to be forgotten. It was soon found preferable to administer it at bedtime to avoid the mild (central) nausea that might occur 3-4 hours later. Some patients with more prolonged nausea of late onset avoid this if it is taken earlier, with the evening meal.

Controls: At the time chloroquine was started, complete skeletal and general examination, fluoroscopy of the thorax, electrocardiography, Kahn test, blood count, ESR determination, complete urinalysis and necessary radiological studies were carried out. An L.E. cell test was done in unusual cases.

*The initial supplies of chloroquine itself, and later of the capsules used in the "double-blindfold" trial, were provided by Winthrop Laboratories of Canada, Ltd., through the courtesy of Mr. R. V. Hulbert of the Department of Medical Research.

Patients were usually reviewed at monthly intervals until stabilization had occurred, and entries were made at each visit of joint measurements, Hb. value, white cell count and ESR, and complete urinalysis, together with the patient's report on progress.

All this information was tabulated on forms modified from those used for the A.R.A. Cooperative Study of Cortisone in Rheumatoid Arthritis, to conform to the particular needs of the present study.

Unfortunately, facilities for the sensitized sheep cell agglutination test and for the latex reaction were not available until the fourth year of the study.

DELAYED ACTION

There is no early response to chloroquine as there is to cortisone or phenylbutazone. Rarely is a *subjective* favourable response encountered in less than two weeks and, not infrequently, beginning *objective* response is noted only after six to twelve weeks. *Maximum* response may be delayed for six to twelve months. To bridge this gap, and to obtain the best results, standard treatment was also given—particularly the basic program of adequate rest, exercise therapy, salicylates and mild sedation.

To cover the waiting period also, adrenal glucocorticoid therapy was used; but only when necessary, i.e., in those threatened with crippling or loss of wage-earning, at the time chloroquine was started. Steroid therapy was given to 35% of the patients but no cases have been included in Grade I or II improvement in which steroids had recently been in use at the time of assessment.

Concomitant use with chloroquine of either gold or phenylbutazone was strictly avoided because of the proclivity of all three to produce a drug dermatitis, in which case the drug responsible could not be differentiated.

ANALYSIS OF RESULTS

Grade of response: Standards* laid down by the American Rheumatism Association[1] are used throughout this report, with minor amplifications that will be noted when appropriate.

**Stage of Disease*

I. Early (osteoporosis, but no destructive radiological changes; no nodule or tenosynovitis).
II. Moderate (slight cartilage or bone destruction; nodules and tenosynovitis may be present in this and more advanced stages).
III. Severe (cartilage and bone destruction, extensive muscle atrophy, subluxation, ulnar deviation).
IV. Terminal (Stage III plus ankylosis).

(Continued on page 184)

The over-all results of the four-year trial of chloroquine in all types of rheumatoid disease in 125 patients, for a total of well over 200 patient-years, are shown in Table I.

TABLE I.—RESULTS OF CHLOROQUINE THERAPY (A.R.A. CRITERIA)

	R.A. (108 patients)*		*M.S.S.** (17 patients)*	
Grade I 39 patients (36%) (Remission)	71%		4 patients (24%)	71%
Grade II 38 patients (35%) (Major improvement)			8 patients (47%)	
Grade III 12 patients (11%) (Minor improvement)	28%		2 patients (12%)	29%
Grade IV 19 patients (17%) (Unimproved)			3 patients (17%)	

*R.A.—Rheumatoid arthritis.
**M.S.S —Marie-Strümpell spondylitis.

Of the 125 patients, 17 were spondylitics; eight were of juvenile onset; and 10 had concomitant psoriasis. The results in these small sub-groups do not warrant comparative statistical consideration, but were similar to those for the main group of classical rheumatoid arthritis.

In most reports, minor benefit (Grade III) is grouped with Grade I and II as a partial success for the method of treatment under study. For practical purposes, however, I feel that Grade III improvement may be due to natural influences and is tantamount to failure. In this group also are placed those cases in which steroid therapy of one type or another might conceivably be partially responsible for improvement at the time of assessment—even though the patient might otherwise be graded I or II improvement. This diminishes the apparent effectiveness of the total program of treatment, but ensures, as far as possible, that chloroquine is not given too much credit.

Nevertheless, 70% of the patients showed either major improvement (Grade II) or remission (Grade I), both groups being about equal in percentage.

IMPROVEMENT IN PERFORMANCE (Class)

The A.R.A. criteria define no halfway point between the person who is able to work, albeit with discomfort, and the nursing-home type of patient. A new class has been added (Class IIa) for the purpose of this analysis to suit the person who is no longer dependent on others for help, but is not yet able to work.

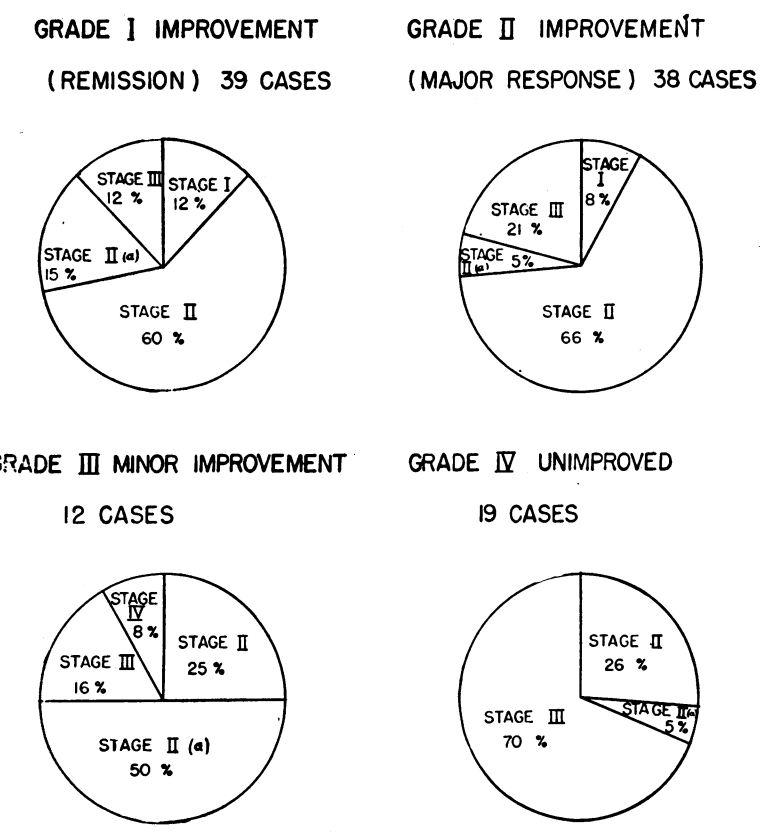

Fig. 1.—Rheumatoid arthritis—108 cases.

Table II shows that improved performance parallels improved objective assessment, and extends beyond it in the case of those (Grades III and IV) classed otherwise as failures, half

Class of functional capacity
I. Completely normal.
II. Adequate (conducts normal activity despite handicap).
III. Limited (performs few or none of the duties of usual occupation or self-care).
IV. Incapacitated (little or no self-care).

Grade of response
I. Complete remission (no positive laboratory or systemic signs of rheumatoid activity; irreversible anatomical changes may persist).
II. Major improvement (minimal residual joint swelling and activity may persist).
III. Minor improvement (joint inflammation only partially resolved).
IV. No improvement or worse (laboratory and clinical data same or worse).

TABLE II.—CHANGE IN CLASS (*i.e.* PERFORMANCE) (USING A.R.A. CORTISONE STUDY CRITERIA—R.A. AND M.S.S.)

Grade of improvement (objective) Performance	*I*	*II*	*III*	*IV*
(1) 4 classes better..	5 (12%)	1 (2%)	——	——
(2) 3 classes better...	5 (12%)	3 (6%)	——	——
(3) 2 classes better...	23 (53%)	6 (13%)	——	——
(4) 1 class better.....	10 (23%)	32 (70%)	11 (80%)	2 (9%)
(5) No change.....	0	4 (9%)	3 (20%)	20 (91%)
Total patients....	43 (34%)	46 (37%)	14 (11%)	22 (18%)

of whom showed a jump of one class. This might well be due, however, to treatment factors other than chloroquine.

RELATION OF OBJECTIVE IMPROVEMENT (GRADE) TO DEGREE OF SEVERITY (STAGE) OF THE ARTHRITIS AT THE START OF CHLOROQUINE TREATMENT

Again the A.R.A. criteria do not entirely suit the purposes of this analysis. The definition implies that a patient with flexion deformity of an important joint should be put into Stage III. A new category, Stage IIa, is defined, therefore, for those patients with deformity of an important joint, such as the knee, relatively recent, and therefore potentially correctable. These patients are more serious problems to treat than Grade II but have a better outlook for improved function than Grade III.

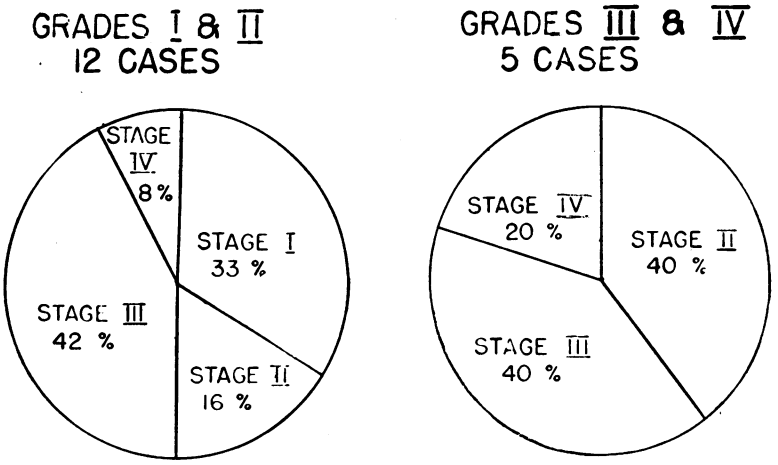

Fig. 2.—Marie-Strümpell spondylitis (17 cases)—response to chloroquine.

As might be predicted for any form of treatment, the majority of those with poor results were those with gross joint damage. However, one-quarter of the "failures" had only moderate disease (Grade II). Most of these had initially improved satisfactorily for months, but were deprived of chloroquine later by toxicity.

On the other hand, it is interesting that only about 10% of those with major benefit (Grades I and II) had low-grade joint inflammation—and that well over a third had major deformities or major damage to joints when chloroquine was started.

Substantially the same degree of benefit is seen in Marie-Strümpell spondylitis. There was a smaller proportion of remissions but a larger number with major improvement—despite the relatively high incidence of more severe degrees of the disease (see Fig. 2).

TABLE III.—GRADE OF RESPONSE AND ERYTHROCYTE SEDIMENTATION RATE

	Remission	*Major benefit*	*Minor benefit*	*No benefit*
Initial E.S.R. (average).....	53	50	83	46
Final E.S.R (average).....	11	32	48	41

Only the E.S.R. is tabulated, but the hæmoglobin levels ran parallel. Objective improvement outstripped the E.S.R. in long-standing arthritis activity in Grade II, but fell short of the E.S.R. improvement in Grade III. The low initial average E.S.R. in Grade IV reflects the proportion of patients with relatively mild disease who eventually had to stop chloroquine because of late toxicity (dermatitis), after early good responses.

RELATION OF OBJECTIVE IMPROVEMENT TO THE EXISTENCE OF RHEUMATOID NODULES AT THE START OF TREATMENT

Of the 108 patients with non-spondylitic arthritis, 20 had subcutaneous rheumatoid nodules. There was remission in eight and major benefit in three, a total of 55% for Grades I and II, compared with 71% for the whole group.

RELATION OF OBJECTIVE IMPROVEMENT (GRADE) TO DURATION OF ARTHRITIS SINCE ONSET OF DISEASE

This factor has been blamed for failure of many other erstwhile "cures" for arthritis—in reality because the treatment was not effective in suppressing the disease itself. Eighty-three per cent of the patients with satisfactory response had had their disease for more than one year and 55% for more than three years when chloroquine was started: 94% of the 36 "failures" had had their disease for more than three years.

RELATION OF OBJECTIVE IMPROVEMENT (GRADE) TO DURATION OF THE ATTACK AT THE START OF CHLOROQUINE (see Fig. 4)

With non-specific types of treatment such as cortisone, it has been my experience that the

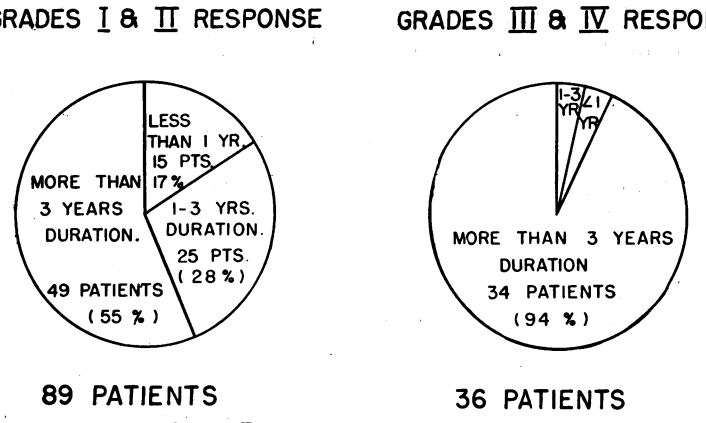

Fig. 3.—Duration of disease (125 patients).

poorest results were to be found in those patients with a history of many years of *persistent* inflammatory activity. Examination of this factor shows that almost as many patients with a good response had had a prolonged duration of the attack as had those with a poor response. Only 19% of good response had had less than a year's duration of rheumatoid activity.

Analysis of Poor Response (Grades III and IV) to Chloroquine

Occurrence of toxicity could not be blamed for 22 out of 36 "failures" (60%). All of them had been able to take the full dosage of ¼ g. daily for six months, or more. In them the factors of severity, and long duration of the disease, and/or of the attack, were comparatively very high.

TABLE IV.—Poor Response to Chloroquine (Grades III and IV—Total 36 Patients)

Cause of failure		
1. On *full dose* for *6 months* or more—22 patients (60%)		
2. *Toxicity* enforced *substandard* dosage after initial grade I or II response.		
Possible explanation of failure	8 = 22%	40%
Probable explanation of failure	6 = 17%	

In the remaining 40% (14 of the 36) failures, the factor of toxicity entered to a variable extent. In 22% (eight patients), full dosage for six months or more was never possible. In the remaining 18% (six patients), major improvement or apparent remission (Grade I or II) had been maintained for 6-30 months before persistently recurring toxicity enforced permanent withdrawal.

Lack of co-operation in treatment cannot be considered a factor because those with inadequate follow-up studies were automatically eliminated from the study.

Analysis of Relapse while on Chloroquine Therapy

Relapses while on therapy are herein defined as those that occurred after a well-maintained initial Grade I or II response. As noted in Table V, relapse occurred late—during the latter half of the first year in four, and in the second and third years in 14 patients. Sixty per cent of these came after *prolonged* administration of less than the standard dosage of ¼ g. of chloroquine diphosphate daily.

Another good reason for relapse was severe or persistent new emotional, physical or infective stress.

TABLE V.—Relapses While on Chloroquine (All Grade I or II Response at the Time)

			Total
1. During *2nd 6 mos.* of therapy	4		
2nd and 3rd year of therapy	14		18
2. While on *full dosage*	5		
Half dosage (previous toxicity)	7		
Quarter dosage (previous toxicity)	6		18
3. Relapse *subsided* with same dosage	6	Within 1-4 mos.	
Relapse *subsided* with increased dosage	10		
Relapse *persisted*	2		18

All but two of the 18 patients responded within one to four months to continuation of

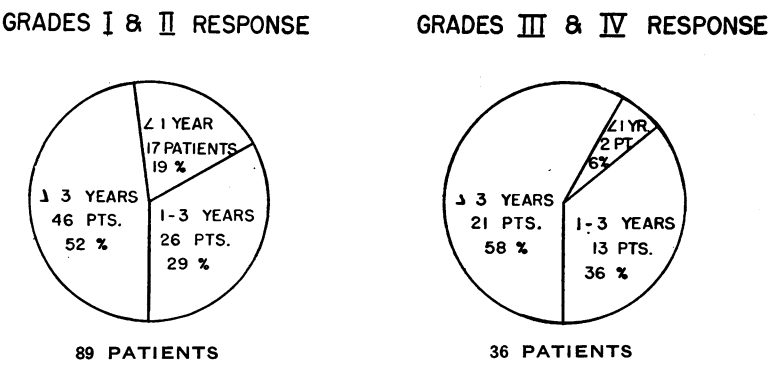

Fig. 4.—Duration of attack (rheumatoid arthritis and Marie-Strümpell spondylitis).

the same or an increased dose of chloroquine. Ten patients who had been kept on a substandard dose of chloroquine because of seeming toxicity were again able to tolerate prolonged full dosage in the face of necessity, with satisfactory response. The severity in the two persistent relapses was mild, carrying them only from Grade I to Grade II response.

ANALYSIS OF RELAPSES AFTER CHLOROQUINE STOPPED

In rheumatoid disease, failure of relapse to occur after withdrawal of what is thought to be an effective remedy would arouse suspicion that the previous improvement was merely coincidental.

Ninety per cent of those with a good response continue with long-term chloroquine therapy. However, in seven patients, treatment was apparently stopped too soon because of seeming remission. In all seven, however, the relapse subsided with resumption of treatment (Table VI).

TABLE VI.—RELAPSES AFTER CHOLORQUINE STOPPED

1. *Reason for stopping*	
Toxicity	6
Remission and toxicity	3
Misunderstanding	3
Remission	9
	21
2. *Relapse occurred*	
Within 3 months	12
After 3 months	9
3. *Relapse subsided*	
Without further chloroquine	6
With further chloroquine	7
Persisted	8

In another six patients, the relapse subsided easily without further chloroquine with only symptomatic treatment, such as a short course of steroid therapy, plus the basic program. Eight patients were unable, because of toxicity, to resume significant doses of chloroquine, and the relapse persists at the date of assessment; these are now included among the "failures".

The majority of relapses occurred within three months of withdrawal, but nine out of 21 (43%) were delayed for up to one year.

REASONS FOR CHLOROQUINE WITHDRAWAL

Five patients out of each of Grades I and II have been off treatment for six months or more without relapse. Whether continued treatment is actually required in the remainder of Grades I and II has not been discovered—nor is it known whether anything is being accomplished by continuing chloroquine in the 14 out of 36 (40%) of Grades III and IV still receiving the drug after many months of relatively unrewarding therapy.

ANALYSIS OF TOXICITY

Very little has been published on the chronic toxicity of chloroquine in humans, at least in the dosage employed in this study of ¼ g. daily for months and years. The meagre information initially available suggested that chloroquine was virtually lacking in toxicity. In the course of this study undesirable (but minor) reactions have turned up with unexpected frequency (Fig. 5).

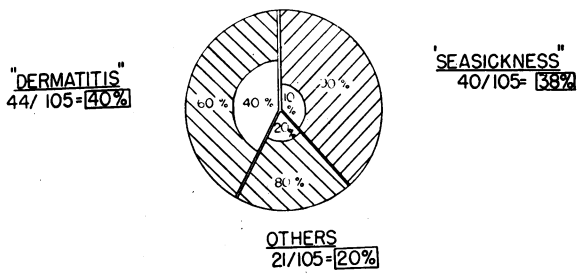

Fig. 5.—Chronic chloroquine toxicity. Total 125 patients; 105 "reactions" in 70 patients. Unshaded area represents proportion of patients unable to take full dosage later.

Out of 125 patients, 70 had a total of 105 reactions that *might* have been due to chloroquine. On the other hand, 76% of these "reactors" were later able to take the full dosage of chloroquine consistently, and only 12 (10% of the whole group of 125 patients) were forced by toxicity permanently to stop chloroquine, although just as many were never able to resume the full dosage of 0.25 g. daily (see Table VII).

Dermatitis (Fig. 5) was not only the numerically greatest nuisance, occurring in 35% of all patients, but 40% of those developing dermatitis were not able subsequently to resume the *full* dosage of chloroquine. Dermatitis usually occurred after several, or many, months of therapy and was the chief toxic factor occasioning permanent withdrawal. On the other hand, since chloroquine is excreted relatively rapidly, i.e. within 10 days or so,[10] when compared to gold, the dermatitis was more of a nuisance than a real threat, and exfoliative dermatitis was not encountered.

TABLE VII.—CHRONIC CHLOROQUINE TOXICITY

Degree	Temporary dose reduction	Prolonged dosage reduction to			
		Half	⅓rd to ¼	Perm. off	Total
Seasickness	29* (23%)	8 (6.5%) 6*	1* (0.8%)	2 (1.6%)	40 (32%)
Dermatitis	20* (16%)	13 (10%) 6*	2 (1.6%) 1*	9 (7%)	44 (35%)
Metrorrhagia	5* (4%)	—	—	—	5 (4%)
Leukopenia (W.B.C. <5000)	5* (4%)	1* (0.8%)	—	—	6 (5%)
Lymphœdema (arm)	1* (0.8%)	2 (1.6%) 1*	1*	—	4 (3%)
Irritated psoriasis	—	4 (3%) 2*	—	—	4 (3%)
Serum sickness (?)	—	1* (0.8%)	—	1 (0.8%)	2 (1.6%)
Total	60* (48%)	29 (23%) 17*	4 (3%) 3*	12 (10%)	105 (80%)

*80 out of 105 reactions (in 70 patients)—able to take full dosage consistently later on 76%
Forced to inadequate dosage—13 ..... 10%

Seasickness (Fig. 5). This syndrome, which seemed to be entirely of central origin, included any one or all of the following—nausea, giddiness, frontal headache and blurring of vision (but *not* hyperacidity dyspepsia)—and was almost as frequent as drug dermatitis. However, it tended to occur early in treatment, and to subside with temporary adjustment downward of dosage. Moreover, 90% of those in whom it occurred were later able to take the full dose consistently, and only two had to stop permanently because of it.

Other possible reactions—About 20% of the annoying episodes listed as possible reactions belong to a miscellaneous group, and most are probably coincidental (see Table VIII).

TABLE VIII.—OTHER POSSIBLE REACTIONS

	Dose alteration			
	Temporarily reduced	Prolonged reduction To half dosage	Eventually stopped	Total
Metrorrhagia	5	—	—	5
Leukopenia (W.B.C. <5000)	5	—	1	6
Lymphœdema (forearm and hand)	1	2	1	4
Psoriasis irritated	2	2	—	4
??Serum sickness	—	1	1	2
	13	5	3	21

Considering the age and sex of the average patient, *metrorrhagia* in five is probably a normal expectancy rather than a toxic effect of chloroquine.

Leukopenia is, however, something quite different. It was encountered only after more than a year's treatment and, because there were no reports of agranulocytosis to chloroquine in the literature, because the differential count remained normal, and because the total count did not fall below 3000, treatment in full dosage was continued. After an uneventful dip of some months' duration, the count again rose to normal in five out of six patients and has remained there. In the sixth patient, the total white cell count stabilized around 3000 per c.mm. but it had been down to 2800 on occasion *before* chloroquine. Nevertheless, since this patient was otherwise in remission, chloroquine was eventually withdrawn four months ago, without change in the white cell count since. Unusual susceptibility to infection was not seen in any of these six patients.

Lymphœdema of the forearm and hand is such an unusual condition that its occurrence in four patients may indicate an unusual toxicity of chronic chloroquine therapy. It was annoying, but subsided in 6-12 months in three patients despite maintenance of chloroquine. In the fourth it persisted, and the patient was not doing well, so Aralen was eventually discontinued—the lymphœdema remains unchanged six months later.

Serum sickness (?). Unusual systemic reactions of the "vasculitis type" occurred in two patients while on chloroquine therapy. Each was receiving other drugs at the time. Fever, polyserositis, and pronounced eosinophilia (70%) characterized the one: she has never received chloroquine since. Recurrent erythema nodosum, glove-and-stocking anæsthesia, leukopenia, fever and lymphadenopathy characterized the other—through a misunderstanding she continued chloroquine for months thereafter, without worsening of the condition. No logical conclusions are to be drawn from these two cases, but they are noted for possible future reference.

SEX RELATIONSHIP OF CHRONIC CHLOROQUINE TOXICITY (Table IX)

Transient (coincidental?) toxicity was two-thirds as frequent in the male as in the female, and toxicity necessitating withdrawal occurred in only two males compared with 10 females, or about one-third as often when the sex incidence of the whole group is taken into consideration.

TABLE IX.—CHRONIC CHLOROQUINE TOXICITY (RELATION TO SEX)

Reduction enforced	*Males* No.	*Males* Proportion of males	*Females* No.	*Females* Proportion of females
Transient	16	41%	44	64%
Half dosage	6	15%	23	33%
⅓ - ¼ dosage	2	5%	2	3%
Complete withdrawal	2	5%	10	15%

Total males —39 = 31% of series.
Total females—86 = 69% of series.

TOXICITY STUDIES IN THE "DOUBLE-BLINDFOLD" GROUP (21 patients)

All were given a mimeographed sheet at the start of therapy (similar to that issued to patients known to be given chloroquine), in which dermatitis and seasickness were noted as the principal side-effects. In March 1957, three and one-half years after the trial was commenced, the sealed letter was opened and the identity of the drug made known to the author.

Five out of 11 on the completely inert placebo, and five out of 19 on chloroquine, had reacted with the seasickness syndrome. However, only one complained of dermatitis while on the placebo and five receiving chloroquine developed dermatitis, one of them rather severely—perhaps because both the drug and sun-bathing were persisted in long after dermatitis appeared.

The high incidence of seasickness in the placebo group shows that the power of suggestion is still an impressive factor to be reckoned with in medicine, but drug dermatitis is a real annoyance in long-term chloroquine therapy.

TREATMENT OF TOXIC REACTIONS TO CHLOROQUINE

Chloroquine is heavily stored[10] in organs such as the liver, spleen, kidney and lungs, from which tissues it only slowly disappears over a period of several weeks. However, the rate and extent of renal secretion is considerably increased by acidification of the urine.

TREATMENT OF:

1. *Drug dermatitis*—withdrawal and re-institution of gradually increasing dosage of chloroquine was all that was necessary in 60% of reactors. More severe reactions were easily managed by glucocorticoid therapy, which served a double purpose in helping with the arthritis as well. Rarely, antihistamines seemed to permit maintenance of adequate chloroquine therapy in patients with persistently recurring dermatitis.

2. *Seasickness syndrome*—a shorter withdrawal period than for dermatitis, followed by gradually increasing doses of chloroquine, was effective in 90% of reactors. Some required in addition the temporary use of an anti-nauseant at the same time as the chloroquine; because of its long duration of action, similar to that of chloroquine, meclizine hydrochloride (Bonamine) has been most frequently used.

Adjustment of timing has proved useful. Most do well to take their daily tablet of chloroquine at bedtime, but some do better to take it earlier in the evening to avoid morning sickness.

3. *Substitution of Plaquenyl* therapy*—Only recently has this derivative, hydrochloroquine, become available, and studies of its value in replacing chloroquine in the treatment of those patients with definite persistent chloroquine toxicity are therefore preliminary. In some patients, there appears to be a complete overlap of toxicity, while others tolerate hydrochloroquine who could no longer tolerate chloroquine. In tropical climates, preliminary studies suggest that hydrochloroquine is just as effective as and better tolerated than chloroquine itself in the control of malaria and amœbiasis. It remains to be seen whether human metabolic ailments, such as rheumatoid disease and discoid lupus erythematosus, respond as well—and also whether toxicity to chloroquine may frequently be escaped by shift to this congener.

ANALYSIS OF RESULTS OF "DOUBLE-BLINDFOLD" STUDY

In the small group of 21 additional patients placed alternately on capsule A or capsule B (capsules being used to disguise the bitter taste of chloroquine), one of each group did not return for a second visit, leaving a total of 19 patients for analysis.

*Kindly provided by Winthrop Laboratories of Canada, through the courtesy of Dr. H. A. Cave.

Of the 10 first given capsule A, none showed a satisfactory response after two to seven months of treatment: eight showed Grade IV response and two a Grade III—and were therefore switched to capsule B.

Of the nine first given capsule B, four eventually showed a Grade II response, and two were Grade I. Because all but two were improved at each assessment, only two were switched to capsule A. These two relapsed badly in two months and were changed back to capsule B.

All 10 of those switched, because of inadequate benefit, from initial capsule A to capsule B are added to those maintained from the start on capsule B. The end result at the time of assessment is shown in Table X.

TABLE X.

	Grade of response				
	I	*II*	*III*	*IV*	*Total*
Capsule A (Placebo)	–	–	3	9	12
Capsule B (Chloroquine)	3	9	5	2	19
Total.....	3	9	8	11	31

Of a total of 12 patients treated with capsule A, there were none with a major response, but 12 out of 19 (63%) of those treated with capsule B showed Grade I or II benefit. This figure, considering the small size of the series, is close to the 70% major improvement (or better) encountered in the main series, and suggested that capsule A was the placebo.

Moreover, in view of the way in which the blindfold trial was set up, the demand from Arthritic Clinics in Vancouver taking part in the trial, but not reported in detail in this paper, should be for much larger supplies of capsule B if it is really an effective agent. Actually, over the years, the demand for capsule B has been about four times that for capsule A. Therefore capsule "A" should be the placebo—which proved to be the case when the Winthrop letter sealed on October 30, 1953, was opened on March 31, 1957.

The clinical material for the double-blindfold study is so small that it does not warrant more detailed analysis.

DISCUSSION

1. HISTORICAL NOTES

An article by Page in the *Lancet* in 1951[2] confirmed a previous French report[3] that quinacrine, a drug useful in malaria, is also useful in a chronic mutilating skin disorder, discoid lupus erythematosus. Perhaps because he was trained in the British fashion to be an astute clinician, he also made note in the same article that, in the course of the (long-term) quinacrine therapy, coincidental chronic synovitis subsided in two patients. Without this fortuitous note, the present long-term study of chloroquine in rheumatoid disease might never have been started.

In the year following the publication of Page's article, two[4, 5] short-term trials of *quinacrine* in small series of patients with rheumatoid disease indicated some benefit. In the meantime, the author had been following up the same clue in a small number of "problem" patients with rheumatoid disease. Unexpectedly good results were encountered in three cases previously very resistant to treatment. Even these three patients were not happy, however, with their jaundiced appearance, and one of them developed a mild exfoliative dermatitis. About this time also, a little-known article (Custer[6]) was encountered reporting a considerable incidence of fatal agranulocytosis in soldiers receiving prolonged quinacrine prophylaxis for malaria (in a rather large dosage). It was therefore decided, early in 1953, to switch from quinacrine (Atabrine or Mepacrine) to chloroquine (Aralen).

Chloroquine has the same very long sidechain as quinacrine, attached at the same place on the complex nucleus, but differs in having a benzene ring removed from the nucleus, and thus is not an acridine dye. It does not pigment the skin, and all reports since its first use for malaria in 1943 have suggested an extremely low rate of toxicity.

During the period of this present rather extensive study, several papers have appeared on the use of chloroquine[7, 8a, 9] in rheumatoid disease, but all have been concerned with relatively short-term results in a small series of cases, rather than its value as a long-term therapeutic agent. Since these studies were initiated subsequent to the present study, little more will be said, as the results published do not conflict with this report.

2. POSSIBLE MECHANISM OF ACTION OF CHLOROQUINE IN RHEUMATOID DISEASE

No good reason why chloroquine should be effective in rheumatoid disease can be given.

Until recent years, interest of the pharmacologist in chloroquine was focused on the metabolism of parasites (malaria, amœbiasis and trichomoniasis), rather than on its effects on the metabolism of the human host of these parasites.

Activity of the antimalarial drugs is known[10] to parallel their ability *in vitro* to antagonize certain pharmacological actions of adenosine, itself an important component of certain coenzymes.

From a purely clinical standpoint, in following up rheumatoid patients on chloroquine therapy, one is struck by the fact that they first feel better in themselves, and look better (sometime in the first few weeks). They then go on to demonstrate that they *are* better by measurable lessening of the swelling, tenderness and protective muscle spasm. This is not the non-specific neutralization of inflammation such as one sees with cortisone—nor is there any primary analgesic action as with phenylbutazone. It appears more like slow neutralization of the disease-producing mechanism itself, since it is accompanied by improvement in the E.S.R. (Table III) and hæmoglobin value.

The latent period of action of a month, or up to many months (if the rheumatoid process has been quite active for a long time), is probably the best clue to the mechanism of action of chloroquine, if one only knew how to go about investigating it. It appears to be a correction of imbalance of some ponderous mechanism, such as one or more enzyme systems, affecting cells throughout the body. A vicious circle of interdependent dystrophy seems gradually to be interrupted, more and more successfully.

The known influence of chloroquine and its congeners on enzyme systems is a very tempting subject for speculation as to its role in the treatment of rheumatoid disease. Inhibition of adenosine activity has already been mentioned. Haydu[11a] in 1949 postulated that quinine congeners should be of help in inhibiting the high level demand for adenosine triphosphate energy ("characteristic of rheumatoid disease") by reason of their power to inhibit adenosine triphosphatase (as do gold and copper salts). In 1953,[11b] he followed this up by showing definite improvement in a series of 28 patients receiving chloroquine for six months in a dosage of 0.5 g. three times a week.

Kurnick[12] calls attention to another physiochemical effect of chloroquine, as well as of quinacrine. If either is added *in vitro* to a system otherwise positive for the L.E. cell phenomenon, the reaction is negated because of the firm combination of the antimalarial with polymerized desoxyribonucleic acid, so that desoxyribonuclease cannot break it down.

Investigation into the influence of chloroquine on normal and disordered human metabolism is in an elementary stage. There are, however, at least a few leads, mainly towards enzyme systems and metabolism at a cellular level. The discovery of cortisone did much to stimulate a new interest in rheumatoid disease and its treatment. Prevailing opinion, however, is that cortisone has a non-specific anti-inflammatory effect; and no facts elucidating the pathogenetic mechanism of rheumatoid disease have emerged from the mass of data now available in regard to cortisone. From a purely clinical standpoint, I feel that investigation of the metabolic activity of chloroquine might prove more rewarding than that of cortisone, because it appears to be almost specific in reversing rheumatoid disease, in the same insidious fashion as the latter has its onset.

Almost since bacteria were discovered, one theory of the etiology of rheumatoid disease has been that it is a systemic response to a chronic infection. It is tempting therefore to suggest that chloroquine acts by suppressing such a chronic infection, as it does malaria and amœbiasis. Amœbiasis[8b] itself, and pleuropneumonia-type organisms, have each been incriminated by an enthusiastic investigator, but not supported by proof. It seems to me that rheumatoid disease is a *final common pathological pathway* capable of being triggered by a variety of stresses, but it is unreasonable to suppose that it is invariably due to an elusive organism chemotherapeutically susceptible to chloroquine in a majority of instances.

3. MATERIAL AND RESULTS

There is little doubt that equally good results would not have been achieved in a series of 125 patients drawn exclusively from indigent patients in out-patient clinics, as those observed in this group of 125 private patients.

Severity of the rheumatoid disease, its duration, and the duration of the attack are the three main factors that appear to determine the effectiveness

of chloroquine. All three of these adverse factors are more apt to be present to a much greater degree in indigent out-patients: this is implied in their attendance at the clinic.

On the other hand (see Figs. 1-4), objectively severe disease, and long duration of the disease or of the attack, were common among those with a good response to chloroquine (remission or major improvement).

The existing basic program of good management was employed to the full—viz. adequate rest and its "mirror-image", planned exercise therapy; adequate salicylates, and sedation; steroid therapy was given where necessary. In the full treatment program for arthritics, each of these has a real place—but we would not be searching frantically for new remedies if the results of this combined treatment were as good as those reported in this series, i.e., those patients in whom long-term chloroquine therapy has been added. Auxiliary measures are particularly important in the early stages because of the long (1-2 months or more) period of waiting until chloroquine begins to have a favourable effect. I do not think that the results would have been significantly different, so far as grade of response is concerned, if steroids had been withheld—except that more of the relatively recent flexion deformities would have been permanent, and exercise therapy less effective. Many reports, including that of the American Rheumatism Association,[13] indicate that cortisone is a non-specific, symptomatic, anti-inflammatory measure. As such, lasting major improvement cannot be ascribed to adjunct cortisone, or one of its congeners used in the *early* stages of choloroquine therapy.

4. Dosage and Duration of Treatment

The optimal dosage appears to be ¼ g. of chloroquine diphosphate daily. In a few patients, this dosage was increased without adding to the benefit, and with a tendency to increased toxicity. In a considerable number (Table V) reduction well below 0.25 g. daily was eventually enforced by the late onset of toxic effects, and relapse followed. This was more frequent in the female (Table IX).

It cannot be over-emphasized that persistence with treatment is necessary. Unless there be undesirable side-effects, the patient is unaware for some weeks that chloroquine is having any influence on the disease. In the light of present experience, a trial of less than three months is probably inadequate—and even if some favourable result is evident at the end of two or three months, maximal benefit is not to be expected for 6-18 months. Given definite encouragement, and in view of the many years' duration indicated by the natural history of rheumatoid disease, the policy I have adopted is to continue chloroquine either indefinitely or for as many years as the disease had already been *active* when chloroquine was started. Unfortunately, toxicity prevented this in some, but my experience to date has shown no other fault with this policy.

Ninety per cent of those with major improvement (Grades I and II) are still on chloroquine, 50% for more than two years.

5. Relapses (Table V)

Relapses on full-dose treatment do occur but commonly there is a good reason for it, such as excessive physical, infective, or psychic stress. On the other hand, other patients undergoing unusual stress while on treatment fail to relapse, and if relapse occurs while on full dosage, it is usually minor and correctable by further prolongation of treatment. Short-term steroid therapy of the "booster type"[14] is a very useful adjunct for these minor flare-ups occurring after initial prolonged remission, since the relapse rate after withdrawal of steroid is very small—suggesting that the relapses are "in miniature", and not major ones invalidating the treatment. The usual cause of relapse while on treatment appears to be the enforced necessity of low dosage resulting from toxicity, usually for dermatitis and usually after the first year of therapy.

6. Poor Results (Table IV)

Over half (60%) of the 29 patients with an unsatisfactory response (Grade III or IV) had the opportunity of six months or more of therapy in full dosage and *never* showed signs of major benefit from chloroquine. These patients were not clinically different from those that did respond, except in a greater incidence of severe disease, or prolonged duration either of the disease or of the attack.

In the remaining 40%, there was a prolonged initial good response, so long as full dosage was possible, but toxicity enforced a low dosage or eventual withdrawal followed by relapse.

7. "DOUBLE-BLINDFOLD" STUDY

Chloroquine lends itself admirably to a "double-blindfold" study. Its bitter taste is easily disguised by dispensing it in capsule form, and the insidious nature of its action is quite in contrast to the rapid symptomatic response to drugs such as prednisone.

While the double-blindfold trial was too small to warrant statistical analysis, it was possible clinically to pick out with reasonable certainty which of the two capsules was chloroquine. Moreover, the type of case selected for this double-blindfold trial, i.e. patients with smouldering arthritis of long standing, is a type that has become sceptical of new remedies, as shown by the uniform ineffectiveness of the placebo.

8. TOXICITY (Fig. 5 and Tables VIII and IX)

Review of the literature gives no indication of the high incidence of minor reactions found in this study—probably because of the dosage used and the prolonged treatment. Definite serious toxicity was not encountered.

Dermatitis is the most annoying, occurring at some time in 40% of the patients. Many of the rashes may well have been coincidental but have been included. It is felt, however, that a true drug dermatitis occurred in 40% of those patients in whom a rash developed, since resumption of full dosage of 0.25 g. daily was subsequently impossible without recurrence of the rash.

On the other hand, only 10% of (the numerically similar) patients developing seasickness syndrome were unable to take the full dosage subsequently. An instruction sheet of the course to be followed should "seasickness" or rash appear was given to each patient at the start of chloroquine therapy. This iatrogenic factor may have been responsible for a large proportion of the nausea, since it occurred also in five out of 11 patients on the placebo capsule in the double-blindfold series.

At no time was there any suggestion of agranulocytosis since the differential count remained normal, but depression of the white cell count occurred for two or three months in six patients, all of whom had been on full doses of chloroquine for over a year. This may be due to some specific metabolic effect of chloroquine, e.g. interference with the depolymerization of desoxyribonucleic acid (an important constituent of the nucleus of leukocytes) but does not seem to imply a dangerous toxicity, since the white cell count eventually returned to normal in five patients *despite continuation of chloroquine in full dosage.* Chloroquine was discontinued in the sixth patient because major improvement had occurred.

Lymphœdema of the forearm and hand in four patients, and a serum sickness type of systemic reaction in two patients, are noted for future reference, but there is no good reason to incriminate chloroquine in their occurrence. Metrorrhagia in five out of 86 female patients in the rheumatoid age group likewise is also probably merely coincidental.

Other antimalarials, particularly hydrochloroquine (Plaquenyl), are under investigation to see whether there is a mandatory overlap of chronic toxicity. There is some indication that there is not.

SUMMARY AND CONCLUSIONS

The first long-term (four-year) study of continuous daily oral chloroquine (Aralen) therapy in rheumatoid disease is reported.

One hundred and twenty-five private patients have been carefully followed up clinically and hæmatologically while receiving well over 200 patient-years of chloroquine therapy.

The results are considered good in 70%, one-half of these cases being in remission. Improved work performance, sedimentation rate, and hæmoglobin levels paralleled the major objective gain in this 70%; 90% of them remain on chloroquine therapy, half for more than two years. Classical peripheral rheumatoid arthritis, spondylitis, arthritis of juvenile onset, and rheumatoid disease with psoriasis, all appeared to respond about equally well.

In this analysis, those failing to show major objective improvement (30%) are rated as failures, although many were subjectively improved. Toxic reactions, seriously affecting the dosage of chloroquine, can be blamed for less than half of these "failures". Of the remainder, many had prolonged consistent rheumatoid activity of severe degree.

The normal dosage was one tablet (0.25 g.) of the diphosphate given daily at bedtime. In 36%, a lesser dosage was at some time necessary, for a considerable period, to avoid toxicity. Permanent withdrawal for this reason was eventually required in 10%.

No definite serious toxic effects were encountered but the number of minor toxic reactions was higher than expected from previous reports, probably because this is also the first large chronic chloroquine toxicity study in humans in the dosage used. Drug dermatitis was the only reaction significantly restricting dosage and treatment, which it did in 16%. Hydrochloroquine (Plaquenyl) is under trial as a substitute. Agranulocytosis has yet to be reported, but leukopenia (with a normal differential count) rising after some weeks to normal, despite continued full-dosage chloroquine therapy, occurred six times in this series.

There is a latent period of one to three months before chloroquine begins to show its favourable effects, and maximum benefit may be delayed for 6-12 months, or even more, in the severe arthritic with long-lasting activity. Short courses of chloroquine are therefore of no value.

A long-term study using the "double-blindfold" technique is also reported. There was no difficulty in determining from the results which was the placebo—but the group is too small for statistical analysis.

It is suggested that chloroquine comes closer to the ideal for long-term, safe control of rheumatoid disease than any other agent now available. Very little is known of its mechanism of action and further investigations of its effects on human metabolism at a cellular level are urgently needed.

REFERENCES

1. STEINBROCKER, O., TRAEGER, C. H. AND BATTERMAN, R. C.: *J. A. M. A.*, 140: 659, 1949.
2. PAGE, F.: *Lancet*, 2: 755, 1951.
3. PROKOTCHUK, A. J.: *In*: 1951 Year book of dermatology and syphilology, edited by M. D. Sulzberger and R. Baer, Year Book Publishers, Inc., Chicago, Ill., 1952, p. 92.
4. FREEDMAN, A. AND BACH, F.: *Lancet*, 2: 321, 1952.
5. ENGESET, A.: *Ibid.*, 2: 537, 1952.
6. CUSTER, R. P.: *Am. J. M. Sc.*, 212: 211, 1946.
7. ESCARPENTER-ORIOL, J., BAYES, A. C. AND GOMEZ, M. S.: *Medizinische*, No. 31: 1083, 1955.
8. (a) RINEHART, R. E.: *Northwest. Med.*, 54: 713, 1955. (b) *Idem*: *Ibid.*, 51: 225, 1952.
9. FREEDMAN, A.: *Ann. Rheumat. Dis.*, 15: 251, 1956
10. GOODMAN, L. S. AND GILMAN, A.: The pharmacological basis of therapeutics, The Macmillan Company, New York, 1955, p. 1167.
11. (a) HAYDU, G. G.: *Am. J. Occup. Therapy*, 3: 177, 1949. (b) *Idem*: *Am. J. M. Sc.*, 225: 71, 1953.
12. KURNICK, N. B.: *A. M. A. Arch. Int. Med.*, 79: 562, 1956.
13. Report of a Co-operative Study Conducted by a Committee of the American Rheumatism Association: *Ann. Rheumat. Dis.*, 14: 325, 1955.
14. BAGNALL, A. W., TRAYNOR, J. A. AND MCINTOSH, H. W.: *Canad. M. A. J.*, 68: 587, 1953.

RÉSUMÉ

Cet article est consacré aux résultats obtenus dans le traitement de la polyarthrite chronique évolutive par la chloroquine ou nivaquine (ARALENE *marque déposée*) administrée à une série de 125 malades pendant quatre ans. Ces malades furent suivis de près au point de vue clinique et hématologique au cours de cette étude. Les résultats furent bons dans 70% des cas, la moitié de ce groupe accusant une rémission. L'amélioration se fit sentir dans la capacité de travail, la vitesse de sédimentation et l'hémoglobine. La majorité de ces malades continuent à prendre de la chloroquine, la moitié d'entre eux en prend depuis plus de deux ans. L'arthrite rhumatoïde périphérique classique, la spondylite, l'arthrite juvénile ainsi que la maladie rhumatoïde avec psoriasis ont toutes semblé réagir avec autant de succès. Les cas qui ne montrèrent pas une forte amélioration objective (30% de la série) furent considérés comme des échecs même si plusieurs d'entre eux accusèrent une amélioration subjective. Les réactions toxiques exigeant une modification de la posologie du médicament, ne furent responsables que pour moins de la moitié de ces échecs. Parmi les autres, plusieurs subirent une recrudescence grave et prolongée de la maladie.

Le médicament fut administrée sous forme de diphosphate à raison d'un comprimé (0 g. 25) chaque soir au coucher. On dut diminuer la dose dans 36% des cas pendant assez longtemps afin d'éviter les manifestations toxiques. Dans 10% des cas, on dut complèment abandonner la médication, pour cette raison. Bien qu'on n'eut à déplorer aucune manifestation toxique grave, les petites réactions furent cependant plus nombreuses qu'on ne s'y attendait, probablement parce que ce travail constitue le premier rapport d'une telle ampleur sur l'emploi de la chloroquine chez l'humain à une dose aussi élevée. La dermatite médicamenteuse fut la seule raison de quelque importance pour modifier la dose et le traitement (16% des cas). On cherche actuellement à employer l'hydrochloroquine comme substitut. L'agranulocytose ne s'est pas encore manifestée mais une leucopénie à différentielle normale, revenant au taux habituel après quelques semaines en dépit d'une dose non modifiée, s'est présentée dans cinq cas.

L'action du médicament ne se fait sentir qu'après une période latente d'un à trois mois, le plein effet ne peut être atteint avant 6 à 12 mois, même plus chez les arthritiques dont les lésions sont en activité depuis longtemps. L'administration du produit pour une courte durée ne sert à rien. Au cours d'une expérience où le médicament et un succédané inerte, présentés tous deux sous une forme identique furent administrés au groupe, on eut aucune difficulté à reconnaître par ses effets, quel comprimé contenait le produit actif. Les chiffres ne sont pas encore assez élevés pour se prêter à l'analyse statistique. L'auteur suggère que la chloroquine se rapproche plus de la médication idéale pour emploi prolongé et sûr comme contrôle de la P.C.E. que n'importe quelle autre, employée jusqu'à présent. On connait mal le mécanisme de son action; les recherches de ses effets sur le métabolisme humain à l'échelle cellulaire sont d'une nécessité immédiate.

THE SPECIFICITY OF THE KVEIM REACTION

Nelson and Schwimmer (*J. Invest. Dermat.*, 28: 55, 1957) report the results of the Kveim test in 335 patients. Among 234 persons who did not have sarcoidosis, only two false positive Kveim reactions were observed. Included among these 234 patients were 99 patients with active tuberculosis, only one of whom showed a positive Kveim test. False positives occurred in up to 6% of cases. This was considered satisfactory for a crude biologic test. The authors emphasize the importance of doing frequent reactivity and specificity tests on the test material. Reports of large numbers of false positives in other series are due to the use of antigenic material which has lost its specificity.